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REMARKS

Claims 26-77 remain pending in the application. Claims 26-57 were considered in the pending Office Action. Claims 58-77 were added in the afore-mentioned Amendment of June 30, 2003.

Reconsideration of the subject application in view of the following remarks is respectfully requested.

The Office Action: Rejections Under 35 U.S.C. §103

Hauer *et al.* in combination with Hamied *et al.*.

The pending Office Action has rejected Claims 26-33 and 36-57 under 35 U.S.C. §103(a) as allegedly being unpatentable over Hauer *et al.* (5,342,625, hereinafter referred to as '625) in view of Hamied *et al.* (5,929,030, hereinafter referred to as '030), or vice versa.

The person skilled in the art would not be motivated to combine '625 and '030.

Applicants respectfully traverse the present rejection for the reasons set forth herein below. Applicants' claims include elements that are neither disclosed nor suggested by the combination of '625 and '030. To illustrate Applicants' position, the discussion herein addresses the pending rejections, according to the suggestion of Examiner Page, as if such rejections were asserted against the claims as presented in the afore-mentioned Supplementary Amendment.

'625 describes pharmaceutical compositions comprising cyclosporin as active ingredient. These compositions are described as microemulsion pre-concentrates and further as "appropriately" comprising a hydrophilic phase, a lipophilic phase, and a surfactant (column 5, line 57 and column 6, lines 45-50). While '625 provides virtual laundry lists of possible

components for the hydrophilic and lipophilic phases and of possible surfactants, it is stated that each is selected with an eye to the active ingredient – cyclosporin (column 8, lines 25-33, column 9, lines 40-47, column 12, lines 42-48). In fact, no other active ingredient is contemplated in '625.

EXHIBIT C shows the chemical structure of cyclosporin. This cyclic polypeptide consists of eleven amino acids. Cyclosporin exhibits immunosuppressive activity. It is a lipophilic and highly hydrophobic compound. Most cyclosporins are soluble in methanol, ethanol, acetone, ether, and chloroform and slightly soluble in water and saturated hydrocarbons.

Taxol is entirely different from cyclosporin – chemically, structurally, and biologically.

EXHIBIT D shows the chemical structure of taxol. Taxol (commercially sold under the name of Paclitaxel) is a diterpenoid compound that contains a complex taxane ring as its nucleus. It contains only one amide bond in its side chain. It is used in cancer treatments. Taxol has *limited* solubility in methanol.

The application under examination is directed to a storage-stable, self-emulsifying, non-aqueous preconcentrate of a taxane in a microemulsion.

The chemical structures shown in EXHIBITS C and D are markedly and significantly different. Cyclosporin and taxol are two distinct compounds that exhibit dissimilar solubilities, pharmacokinetics, and activities, as well. As a result, their respective absorption, fate, and excretion in a human subject, for example, will vary upon administration. '625 does not contemplate *any* other active agent than cyclosporin, and the preconcentrate it describes is prepared with the goal of optimizing a formulation for cyclosporin. The marked differences between cyclosporin and taxol (chemical, structural, pharmacological, and functional), along with '625's method of proceeding in the preparation of the preconcentrate of the active agent

(cyclosporin) that is entirely focused on the optimization of conditions for that same agent, and none other, virtually precludes the skilled person from looking to '625 and using the '625 formulation "recipe" in preparing a taxane preconcentrate. At best, the person of ordinary skill in the art would look to '625 for guidance in preparing formulations for Cyclosporin B, Cyclosporin C, and closely related large ring amides – active agents with significantly different solubilities, absorption, fate, and excretion than taxol.

'030 describes the preparation of a preconcentrate or microemulsion, wherein a water-insoluble active substance is first dissolved in a lipophilic phase, and *not* the hydrophilic phase. '030 identifies its invention as *particularly* useful for cyclosporins: "The invention is particularly useful with the cyclosporins, e.g. cyclosporin A, ..." (column 2, lines 62-66), and the Examples presented in '030 all include Cyclosporine A as the active substance.

While '030 *mentions* taxol as a possible water-insoluble substance for inclusion in the composition of the invention, it fails to provide any guidance with respect to how, or data to show that, taxol could be formed into a stable microemulsion. Undue experimentation would be required on the part of the person of ordinary skill in the art in order to determine the components for inclusion in a composition according to '030 comprising *taxol* as its active ingredient. This is emphasized, for example, by '030's preference for the inclusion of lecithin in the composition of the disclosed invention: "Hydroxylated lecithins are particularly suitable, especially when component (a) is a cyclosporin..." (column 3, lines 45-46). In fact, the inclusion of lecithin in '030's composition is stated as "necessary to obtain the significant advantages of the invention" (column 2, lines 47-50). Lecithin is a highly ionic phospholipid surfactant. This would prompt the skilled person, in following the teachings of '030, to use lecithin in preparing taxol microemulsions.

In contrast, the claimed storage-stable, self-emulsifying, non-aqueous taxane preconcentrate does *not* include a lecithin; rather, it comprises a non-ionic surfactant(s). Since '030 essentially requires lecithin as a component in its composition, it teaches *away* from the claimed preconcentrate. Thus, the person of ordinary skill in the art attempting to combine the teachings of '625 with those of '030 would not include one or more non-ionic surfactants in the preparation of a taxol microemulsion and would be motivated to include lecithin or other ionic surfactants.

The claimed invention is not obvious in view of '625 in combination with '030.

'030 includes *no* bioavailability data whatsoever. Accordingly, one would not have the expectation that use of the same formulations disclosed for cyclosporin would provide practical bioavailability. In contrast, the high bioavailability (of taxane, upon administration) is an unexpected feature of the present invention. As one of skill in the art would recognize, the mere capability of preparing a stable formulation, without more, is not enough to establish utility for a pharmaceutical formulation. Rather, in addition to stability, a pharmaceutical formulation must be capable of demonstrating significant bioavailability.

'030 certainly does not address the previously identified significant differences between cyclosporin and taxol, nor does it address how the skilled person would select the appropriate components for a composition comprising taxol, such choice being dictated in large part by these recognized differences, *let alone* a stable composition comprising taxol that ensures high bioavailability of taxol upon administration, even if said skilled person has access to the information in '030.

Thus, claims 26-33, 36-57, and 58-77 are not obvious in view of any combination of '625 and '030.

Hauer *et al.* in combination with Hamied *et al.* in further combination with Rathi *et al.*.

Claims 26-33 and 36-57 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Hauer *et al.* (5,342,625, hereinafter referred to as '625) in combination with Hamied *et al.* (5,929,030, hereinafter referred to as '030) and further in combination with Rathi *et al.* (6,004,573, hereinafter referred to as '573) or Hamied *et al.* (5,929,030, hereinafter referred to as '030) in combination with Hauer *et al.* (5,342,625, hereinafter referred to as '625) and further in combination with Rathi *et al.* (6,004,573, hereinafter referred to as '573).

The claimed invention is not obvious in view of '625 in combination with '030 in further combination with '573 or '030 in combination with '625 in further combination with '573 .

Applicants respectfully traverse the present rejection for the reasons set forth herein below. To illustrate Applicants' position, the discussion herein addresses the pending rejections, according to the suggestion of Examiner Page, as if such rejections were asserted against the claims as presented in the afore-mentioned Supplementary Amendment.

'573 discloses an aqueous biodegradable polymeric drug delivery composition having thermal gelation properties and comprising an aqueous phase with a drug and a biodegradable ABA-type block copolymer uniformly within. This biodegradable composition is utilized for diffusion-controlled release of drug. '573 presents *in vitro* (watchglass in beaker) drug release

data (Examples 7 and 8) showing a relatively continuous release of the drug over a period of one week to 50 days, with the initial amount of drug released being relatively low in quantity. This demonstrates '573's desire to obtain zero-order release kinetics equal to an essentially constant release over time.

The claimed invention is *not* a conventional drug release system; rather, it is a self-emulsifying system that provides a higher concentration of active agent more immediately (25% to 60% within two hours from administration, for example; in comparison with less than 10% during the first 24 hours after administration for a composition according to '573 (Figure 4 of latter). Figure 1 of the instant application provides the pharmacokinetic profile obtained for a paclitaxel preconcentrate according to the invention. This constitutes *in vivo*, not *in vitro*, bioavailability data supporting a statement of rapid high active substance (taxane) bioavailability for the preconcentrates of the claimed invention. *In vivo* (within a living organism) data is, of course, far superior to *in vitro* (in a test tube or other artificially designed environment) data, as it constitutes a more realistic indicator of results that would be obtained, for example, upon administration of an active agent to a human being. Thus, '573 and the application under investigation are directed to solutions of two entirely different problems – the sustained release of an active species via a diffusion-controlled mechanism from within a complex polymeric structure vs. the enhanced bioavailability of a poorly soluble active species (taxane).

As previously discussed, the combination of '625 and '030 does not render obvious the invention of the application under investigation. The unsupported combination of these two references with regard to rendering obvious the claimed invention is not corrected by additional consideration of '573. Specifically, '030 does not address how the skilled person would select the

appropriate components for a composition comprising taxol, *let alone* a composition comprising taxol that ensures high bioavailability of taxol upon administration.

The person skilled in the art would not be motivated to further combine '625 and '030 with '573.

'573 states that "The combination of the hydrophobic A-blocks and hydrophilic B-block render the block copolymer amphiphilic in nature." (column 11, lines 1-3). The diffusion-controlled drug delivery composition of '573 comprises an aqueous phase containing the drug and the biodegradable block copolymer, the latter of which has the formula PLGA-PEG-PLGA, wherein PLGA is hydrophobic and PEG is hydrophilic. This is in marked contrast to '030, which *specifically* calls for the dissolution of active substance in a lipophilic phase, and *not* the hydrophilic phase. Thus, the person of ordinary skill in the art would not be motivated to combine the teachings of '573, whose goal is the sustained release of an active agent, rather than the enhanced bioavailability of a water-insoluble species, with those of '030. Furthermore, the skilled person would find little reason to combine the teachings of '625 with those of '030 and those of '573, as he would be disinclined to combine the teachings of '030 with those of '625 and those of '573. Thus, claims 26-33, 36-57, and 58-77 are not obvious in view of '625 in combination with '030 in further combination with '573 or '030 in combination with '625 in further combination with '573.

Hauer *et al.* in combination with Hamied *et al.* in further combination with Sime *et al.*.

In the pending Office Action, Claims 34-35 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Hauer *et al.* (5,342,625, hereinafter referred to as '625) in combination with Hamied *et al.* (5,929,030, hereinafter referred to as '030) and further in combination with Sime *et al.* (WO96/35415, hereinafter referred to as '415) or Hamied *et al.* (5,929,030, hereinafter referred to as '030) in combination with Hauer *et al.* (5,342,625, hereinafter referred to as '625) and further in combination with Sime *et al.* (WO96/35415, hereinafter referred to as '415).

The claimed invention is not obvious in view of '625 in combination with '030 in further combination with '415 or '030 in combination with '625 in further combination with '415.

Applicants respectfully traverse the present rejection for the reasons set forth herein below. To illustrate Applicants' position, the discussion herein addresses the pending rejections, according to the suggestion of Examiner Page, as if such rejections were asserted against the claims as presented in the afore-mentioned Supplementary Amendment.

'415 describes the use of sesquiterpene as a medicament. According to '415, sesquiterpene is used in the preparation of a composition in order to stabilize a drug compound *in vivo* or *in vitro* when the drug compound exhibits a specific instability in the presence of one or more oxidative enzymes. The pharmaceutical compositions described in '415 are *not* microemulsions. While taxol is mentioned as a possible drug for inclusion in a composition together with sesquiterpene, there is no disclosure of microemulsion formulations, nor does '415 provide discussion or indication of bioavailability (let alone high bioavailability) of taxol as the result of administration of such a composition. In fact, *no in vivo* data for taxol is provided;

rather, a secondhand account of *in vivo* efficacy for a felodipine composition is recounted. Felodipine is a calcium channel antagonist with a very different chemical structure, as well as biology and function, from taxol. Thus, the person of ordinary skill in the art would be unable to make any assumptions about the bioavailability of taxol administered via a composition according to '415 based on the secondhand account of a positive inhibitory effect on the metabolism of felodipine upon administration with sesquiterpene. In effect, the skilled person simply would not look to '415 to solve the problems addressed by the present invention (i.e., low solubility, difficulty of formulation, high bioavailability).

The application under examination, on the other hand, is specifically directed to a storage-stable, self-emulsifying, non-aqueous preconcentrate of a taxane in a microemulsion. The claimed preconcentrate has a high bioavailability (of taxane, upon administration.) In marked contrast to '415, firsthand *in vivo* bioavailability data is presented for a paclitaxel microemulsion concentrate in Example 6 of the specification.

As previously discussed, no combination of '625 and '030 renders the claimed invention obvious. The addition of a sesquiterpene does not overcome such unsupported combination. Specifically, it does not teach how the skilled person would select the appropriate components for a taxane preconcentrate, *let alone* such a preconcentrate including non-ionic surfactant and having high bioavailability of taxane upon administration.

The person skilled in the art would not be motivated to further combine '625 and '030 with '415 or '030 and '625 with '415.

As previously discussed, the skilled person would not find motivation in the teachings of '625 and '030 to combine the two. Furthermore, the teachings of '415 would not motivate the

skilled person to combine them with those of '625 and '030. In the first, '415 does not teach microemulsions. Secondly, the only compound of which '415 speaks (and speaks secondhand, at that) with regard to bioavailability is felodipine, a compound that is structurally, biologically, pharmacologically, and functionally different from taxol. Thus, there is no reason why the skilled person would consider the teachings of '625 and '030 in combination with those of '415 with the expectation of achieving a storage-stable, self-emulsifying non-aqueous preconcentrate of taxane in a microemulsion, let alone such a preconcentrate having high taxane bioavailability. Consequently, claims 34-35 and 58-77 are not obvious in view of '625 in combination with '030 in further combination with '415 or '030 in combination with '625 in further combination with '415.

Hauer *et al.* in combination with Hamied *et al.* in further combination with Rathi *et al.* in further combination with Sime *et al.*.

In the pending Office Action, Claims 34-35 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Hauer *et al.* (5,342,625, hereinafter referred to as '625) in combination with Hamied *et al.* (5,929,030, hereinafter referred to as '030) and further in combination with Rathi *et al.* (6,004,573, hereinafter referred to as '573) and further in combination with Sime *et al.* (WO96/35415, hereinafter referred to as '415) or Hamied *et al.* (5,929,030, hereinafter referred to as '030) in combination with Hauer *et al.* (5,342,625, hereinafter referred to as '625) and further in combination with Rathi *et al.* (6,004,573, hereinafter referred to as '573) and further in combination with Sime *et al.* (WO96/35415, hereinafter referred to as '415).

The claimed invention is not obvious in view of '625 in combination with '030 in further combination with '573 in further combination with '415 or '030 in combination with '625 in further combination with '573 in further combination with '415.

Applicants respectfully traverse the present rejection for the reasons set forth herein below. To illustrate Applicants' position, the discussion herein addresses the pending rejections, according to the suggestion of Examiner Page, as if such rejections were asserted against the claims as presented in the afore-mentioned Supplementary Amendment.

As previously discussed, no combination of '625 and '030 renders the claimed invention obvious. As likewise mentioned above, the addition of the teachings of '573 to those of '625 and '030 does not overcome the defects of the combination of '625 and '030 with respect to their inability to render obvious the claimed invention. The further addition of the teachings of '415 similarly fails to overcome the defects of the combination of '625 and '030 and '573 with respect to their inability to render obvious the claimed invention. In effect, even the combination of all four cited references fails to teach a storage-stable, self-emulsifying, non-aqueous preconcentrate of a taxane in a microemulsion, the preconcentrate having a high bioavailability of taxane upon administration. Furthermore, the combination of these references does not provide motivation to prepare the claimed preconcentrate in a microemulsion with the expectation of having high bioavailability upon oral administration.

Summary

Applicants contend that the burden necessary for establishing a *prima facie* case of obviousness, as alleged in the pending Office Action, has not been met. Specifically, the claimed preconcentrate is not taught by any of the Action-cited combinations of the art. Thus,

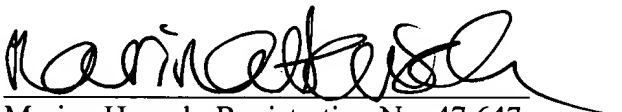
each outstanding rejection for obviousness asserted in the pending Office Action which relies on '625 and '030 or '625 and '030 and '573 or '625 and '030 and '415 or '625 and '030 and '573 and '415 fails to establish a *prima facie* case of obviousness primarily because, even if successfully combined, all of the claim limitations expressed in the claims are neither taught nor suggested by the presently cited art. .

Applicants further contend that there is insufficient motivation, either explicit or implicit, to combine the teachings of '625 and '030 or '625 and '030 and '573 or '625 and '030 and '415 or '625 and '030 and '573 and '415, as was done in the pending Office Action to support the obviousness rejections.

Accordingly, it is respectfully submitted that as a result of the above remarks, all of the claims presently pending in this application, namely claims 26-77, are in condition for allowance, and such action is earnestly solicited.

Should the Examiner believe that a personal or telephonic interview may facilitate resolution of any remaining matters, Applicant's representative may be contacted at the number indicated below.

Respectfully submitted,



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FORM PTO-1083

PATENT
Attorney Docket No. 402076

In re Application of: PARIKH et al.
Application No. 09/281,430
Filed: March 30, 1999
For: ANTICANCER COMPOSITIONS

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Transmitted herewith is a supplemental amendment in the subject application.

☐ Applicants claim small entity status of this application under 37 CFR 1.27.

☒ Petition for Extension of Time
- ☐ Applicants petition for a one-month extension of time under 37 CFR 1.136, the fee for which is $110.00 (enclosed).
- ☒ Applicants believe that no petition for an extension of time is necessary. However, to the extent that such petition is deemed necessary, Applicants hereby petition for a sufficient extension of time to render the present submission timely. Please charge Deposit Account No. 12-1216 for the appropriate petition fee.

☐ No additional claim fee is required.

☐ Other:

The claim fee has been calculated as shown below:

					Small Entity		Other Than A Small Entity	
	Claims Remaining After Amendment		Highest Number Previously Paid For	Extra Claims	Rate	Addit. Claim Fee	Rate	Addit. Claim Fee
Total	50	Minus	32	=18	x 9=	$	x 18=	$324.00
Independent	11	Minus	11	=0	x 42=	$	x 84=	$
☐ First Presentation of Multiple Claim					+ 140=	$	+ 280=	$
					Total	$	Total	$324.00

☒ Please charge my Deposit Account No. 12-1216 in the amount of $324.00. A duplicate copy of this sheet is attached.

☐ A check in the amount of $ is attached.

☒ The Commissioner is hereby authorized to charge any deficiencies in the following fees associated with this communication or credit any overpayment to Deposit Account No. 12-1216. A duplicate copy of this sheet is attached.
- ☒ Any filing fees under 37 CFR 1.16 for the presentation of extra claims.
- ☒ Any patent application processing fees under 37 CFR 1.17.

Respectfully submitted,

Shannon Schemel

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Date: June 30, 2003
SDS:ves

PATENT
Attorney Docket No. 402076

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PARIKH et al.

Art Unit: 1615

Application No. 09/281,430

Examiner: T. Ware

Filed: March 30, 1999

For: ANTICANCER COMPOSITIONS

SUPPLEMENTAL AMENDMENT

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Please enter the following amendments and consider the following remarks.

CLAIM AMENDMENTS

Claims 1-25 (cancelled).

26 (previously amended): A storage-stable, self-emulsifying, and non-aqueous, preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants;

up to 35% w/w diethylene glycol monoethylether; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, forms a liquid having an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

27 (previously amended): The self-emulsifying preconcentrate of claim 26, wherein the carrier system consists of 15 to 75% w/w of the hydrophobic component.

28 (previously amended): The self-emulsifying preconcentrate of claim 26, wherein the carrier system consists of up to 30% w/w of the hydrophilic component.

29 (previously amended): A storage-stable, self-emulsifying, and non-aqueous preconcentrate of at least one taxane in a composition consisting essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, 1,2-propylene glycol, ethanol, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

30 (previously amended): The preconcentrate of claim 29, wherein the hydrophilic component is selected from the group consisting of 1,2-propylene glycol and ethanol.

31 (previously added): An orally administrable pharmaceutical composition consisting essentially of the preconcentrate of claim 29 in a pharmaceutically acceptable carrier or diluent.

32 (previously added): A parenterally injectable pharmaceutical composition consisting essentially of the preconcentrate of claim 29 in a pharmaceutically acceptable diluent.

33 (previously added): The preconcentrate of claim 29 filled in a soft or hard gelatin capsule.

34 (previously amended): The preconcentrate of claim 29, wherein the preconcentrate also includes an inhibitor of P-glycoprotein transport system or an inhibitor of cytochrome P450 enzyme.

35 (previously amended): The preconcentrate of claim 29, wherein the preconcentrate comprises grapefruit extract or a component thereof.

36 (previously amended): The preconcentrate of claim 29, wherein the taxane is paclitaxel or docetaxel.

37 (previously amended): A method of orally or parenterally administering a taxane to a subject in need of same comprising administering a dose of a storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane consisting essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

38 (previously amended): The method of claim 37, wherein the taxane is solubilized in the preconcentrate.

39 (previously added): A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component.

40 (previously added): The preconcentrate of claim 39, wherein the preconcentrate forms a liquid having an average droplet size of at most 10 microns when mixed with water or simulated gastric fluid.

41 (previously added): The preconcentrate of claim 40, wherein a dose of the preconcentrate has a taxane bioavailability of 25 to 60% upon oral administration.

42 (previously added): The preconcentrate of claim 41, wherein at least a portion of the hydrophilic component consists of ethanol, such that the carrier system contains at least 6% w/w ethanol.

43 (previously added): The preconcentrate of claim 39, wherein the preconcentrate, when mixed with an aqueous medium and heated to 20-37° C, forms a liquid having an average droplet size of at most 10 microns.

44 (previously added): The preconcentrate of claim 43, wherein the preconcentrate, upon oral administration, forms a microemulsion *in situ* in the gastrointestinal tract.

45 (previously amended): A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component; and

6% to 40% w/w of a hydrophilic component, at least a portion of which hydrophilic component consists of ethanol, such that the carrier system contains at least 6% w/w ethanol.

46 (previously added): The preconcentrate of claim 45, wherein the surfactant component consists of one or more surfactants selected from the group consisting of polyoxyethylene-sorbitan-fatty acid esters, polyoxyethylene fatty acid esters, α-tocopherol, α-tocopheryl polyethylene glycol succinate, α-tocopherol palmitate, α-tocopherol acetate, PEG glyceryl fatty acid esters, propylene glycol mono- or di-fatty acid esters, sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene co-polymers, glycerol triacetate, monoglycerides, and acetylated monoglycerides.

47 (previously added): The preconcentrate of claim 46, wherein the preconcentrate forms a liquid having an average droplet size of at most 10 microns when mixed with water or simulated gastric fluid.

48 (previously added): The preconcentrate of claim 47, wherein a dose of the preconcentrate has a taxane bioavailability of 25 to 60% upon oral administration.

49 (previously added): The preconcentrate of claim 45, wherein the preconcentrate, when mixed with an aqueous medium and heated to 20-37° C, forms a clear liquid having an average droplet size of at most 10 microns.

50 (previously added): The preconcentrate of claim 49, wherein the preconcentrate, upon oral administration, forms a microemulsion *in situ* in the gastrointestinal tract.

51 (previously amended): A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion comprising a taxane dissolved in a carrier system, which carrier system consists essentially of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more surfactants selected from the group consisting of a polyoxyethylene-sorbitan-fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene castor oil derivative, α-tocopherol, α-tocopheryl polyethylene glycol succinate, α-tocopherol palmitate, α-tocopherol acetate, a PEG glyceryl fatty acid ester, a propylene glycol mono- or di-fatty acid ester, a sorbitan fatty acid ester, a polyoxyethylene-polyoxypropylene co-polymer, glycerol triacetate, a monoglyceride, an acetylated monoglyceride, and combinations of any thereof; and

6% to 40% of a hydrophilic component, at least a portion of the hydrophilic component consisting of ethanol, such that the carrier system contains at least 6% w/w ethanol.

52 (previously added): The preconcentrate of claim 51, wherein a dose of the preconcentrate has a taxane bioavailability of 25 to 60% upon oral administration.

53 (previously amended): An injectable pharmaceutically acceptable composition consisting essentially of a storage-stable, self-emulsifying, and non-aqueous preconcentrate of at least one taxane in a composition consisting essentially of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component; and

6% to 40% w/w of a hydrophilic component,

wherein (a) at least a portion of which hydrophilic component consists of ethanol, such that the composition contains at least 6% w/w ethanol, (b) the surfactant component of the composition consists of one or more non-ionic surfactants, or (c) conditions (a) and (b) apply.

54 (previously added): A storage-stable, self-emulsifying, and non-aqueous, preconcentrate of a taxane in a microemulsion consisting of a taxane dissolved in a carrier system, which carrier system consists of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants;

up to 35% w/w diethylene glycol monoethylether; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, forms a liquid having an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

55 (previously added): A storage-stable, self-emulsifying, and non-aqueous preconcentrate of at least one taxane in a composition consisting of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, 1,2-propylene glycol, ethanol, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

56 (previously added): A method of orally or parenterally administering a taxane to a subject in need of same consisting of administering a dose of a storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane consisting of:

10 to 80% w/w of a hydrophobic component selected from the group consisting of a triglyceride, a diglyceride, a monoglyceride, a free fatty acid, a fatty acid ester, a fish oil, a vegetable oil, and combinations thereof;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component selected from the group consisting of a hydroxyalkane, a dihydroxyalkane, a polyethylene glycol having an average molecular weight of at most 1000, and combinations thereof;

wherein the preconcentrate, when mixed with water or simulated gastric fluid, gives an average droplet size of at most 10 microns, and a dose of the preconcentrate has a taxane bioavailability of 25 to 60% of the taxane in the dose upon oral administration.

57 (previously added): A storage-stable, self-emulsifying, and non-aqueous preconcentrate of a taxane in a microemulsion consisting of a taxane dissolved in a carrier system, which carrier system consists of:

10 to 80% w/w of a hydrophobic component;

20 to 80% w/w of a surfactant component consisting of one or more non-ionic surfactants; and

up to 40% w/w of a hydrophilic component.

58 (new): The preconcentrate of claim 29, wherein the taxane is paclitaxel and is present in an amount of from 1.36% to 5.7% by weight of the preconcentrate.

59 (new): The preconcentrate of claim 29, wherein the composition consists of 15 to 75% w/w of the hydrophobic component.

60 (new): The preconcentrate of claim 29, wherein the hydrophobic component consists of a medium chain triglyceride.

61 (new): The preconcentrate of claim 29, wherein the hydrophobic component consists of propylene glycol dicaprylate/caprate and is present in an amount of from 31.2 to 34.9% by weight of the preconcentrate.

62 (new): The preconcentrate of claim 29, wherein the surfactant component consists of polyoxyl 40 hydrogenated castor oil, PEG-8 glyceryl caprylate/caprate, and glycerol monocaprylate.

63 (new): The preconcentrate of claim 62, wherein the polyoxyl 40 hydrogenated castor oil is present in an amount of from 32.2 to 38.8% by weight of the preconcentrate.

64 (new): The preconcentrate of claim 62, wherein the PEG-8 glyceryl caprylate/caprate is present in an amount of from 8.1 to 9.7% by weight of the preconcentrate.

65 (new): The preconcentrate of claim 62, wherein the glycerol monocaprylate is present in an amount of from 11.3 to 13.6% by weight of the preconcentrate.

66 (new): The preconcentrate of claim 29, wherein the hydrophobic component consists of caprylic/capric triglyceride.

67 (new): The preconcentrate of claim 66, wherein the caprylic/capric triglyceride is present in an amount of 28.7% by weight of the preconcentrate.

68 (new): The preconcentrate of claim 26, wherein the taxane is docetaxel.

69 (new): The method of claim 37, wherein the taxane is docetaxel.

70 (new): The preconcentrate of claim 39, wherein the taxane is docetaxel.

71 (new): The preconcentrate of claim 45, wherein the taxane is docetaxel.

72 (new): The preconcentrate of claim 51, wherein the taxane is docetaxel.

73 (new): The composition of claim 53, wherein the taxane is docetaxel.

74 (new): The preconcentrate of claim 54, wherein the taxane is docetaxel.

75 (new): The preconcentrate of claim 55, wherein the taxane is docetaxel.

76 (new): The method of claim 56, wherein the taxane is docetaxel.

77 (new): The preconcentrate of claim 57, wherein the taxane is docetaxel.

REMARKS

Claims 58-77 have been added and are directed to embodiments of the invention. The basis for the new claims may be found in the original specification and claims. For example, the percentages recited in claims 58, 61, 63-65, and 67 are supported by Examples 1-5. No new matter has been added.

The application is considered in good and proper form for allowance. Should there remain any issues outstanding, the Examiner is invited to call the undersigned at her Washington, D.C. office.

Respectfully submitted,

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The Patent Office acknowledges, and has stamped hereon, the date of the receipt of the items checked below:

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Application No.: 09/281,430
Inventor(s): PARIKH et al.

- ☒ Fee Amount $324.00
- ☒ Amendment
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- ☐ Assignment & Fee
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- ☐ Transmittal of Formal Drawings & sheets of drawings
- ☐ Maintenance Fee Address Form
- ☐ Petition Under ☐ & Fee
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- ☐ PTO-1449 (pages) ☐ & documents
- ☐ RCE Transmittal Letter (pages; w/duplicate copy)